VETR CURRENT POLICIES & PROCEDURES

1.0 Introduction (October 2002)

During the Vietnam era (1965-1975) a total of ~9 million individuals served on active duty in the U.S. military and ~3 million of these served in Vietnam. The Vietnam Era Twin Registry was formed to study the genetic and non-genetic factors that affect the health of veterans. The Registry was created from electronic records maintained by the Department of Defense and Department of Veterans Affairs. A computerized record linkage methodology was developed that identified pairs of electronic records that had a reasonable probability of being twins. The algorithm that was used involved the following criteria: males, born between 1939 - 1957, served on active duty during the Vietnam era (the interval 1965-1975), same last name, different first name, same date of birth, and same first 5 digits of the Social Security Number (Eisen et al, 1987; Goldberg et al., 1993). In total 15,711 paired records were identified using the algorithm.

For each set of paired records (that represented a potential twin) the hard-copy military record was retrieved. Using the place of birth and parental names a total of 7,369 twins pairs were identified from the paired records. These twins form the base population for the VET Registry.

1.1 Demographics and Zygosity Assessment (October 2002)

In 1987 an initial survey of all twin pairs was conducted by the VETR. The purpose of this survey was to obtain information on basic demographic and health characteristics and to assign zygosity. In total 10,979 individuals responded to the survey with a pair wise response rate of 64% (n =4,774 pairs). The table below summarizes some of the basic demographics of the VETR.

Demographics	Twisn located throughout the USA
Ascertainment	Twin pairs serving in the military between 1965 to 1975
Twins	All male-male
Number of twins by birth year category	All male-male 1935 - 1939: 36 1940 - 1944: 722 1945 - 1949: 8042 1950 - 1954: 4984 1955 - 1957: 960
Zygosity	52% - Monozygotic 45% - Dizygotic 3% - Indeterminate

2.0 Researcher Access (January 2005)

The VETR is designed as a scientific resource for both VA and non-VA researchers. The VETR welcomes proposals from investigators seeking to include VETR twin pairs in their research. The liaison for this process is the VETR program manager. Although the VETR will try and expedite requests to the greatest possible degree, applicants should be aware that considerable lead-time is

necessary for a proposed project to be reviewed, approved and implemented. Experience has shown that a period of 6 to 12 months from time of initial contact to approval and implementation is not unrealistic. The review and approval process includes informal and formal phases. The informal, or preliminary, phase involves initial contact with the VETR program manager, submission of a letter of intent, and the establishment of an ongoing dialogue about the project with the VETR Director. In order to submit a grant application for funding the investigator must include a letter of support signed by the VETR Director. No grant application can be submitted without this letter. The formal process includes submission of a VETR application and review by the VETR Scientific Advisory Committee (SAC).

Typical time line for project application and review process

Time period	Activity
6 months from grant submission deadline	Initial contact with VETR project manager
3 to 6 months from grant submission deadline	• Submission of letter of intent • Project discussions with VETR • Preliminary data analysis by VETR to determine project feasibility
Simultaneous with submission to a funding agency	Submission of VETR application
Grant agency notice of award and summary statement	Application to be reviewed by VETR SAC

2.1 Safeguarding Participant Data (January 2005)

Because the VETR's very existence rests on the continued participation of the twins, the VETR is vigilant about protecting participants' rights to privacy and the confidentiality of the data they provide. The VETR has implemented a system that strictly limits direct contact between investigators and VETR twins. This system involves the use of approved 3rd party contractors to contact VETR members on behalf of investigators. For example, if a study is collecting data using written questionnaires, the VETR will provide the contractor with the names and addresses of VETR members to contact and administer the survey. Once the data are collected, the contractor returns the data to the VETR and these data are then forwarded to the investigators using study-specific unique identifiers. The names and addresses of VETR members are never shared with the investigators. For clinical protocols that require direct interaction of VETR twins with investigators, an approved 3rd party contractor makes the initial contact with the twins on behalf of the investigator. The purpose of this contact is to introduce the study and obtain signed letters of agreement indicating a willingness to participate from twin pairs. Once these letters of agreement are obtained by the VETR, contact information is released to the investigator to schedule the clinical examinations.

All investigators who work with VETR twins and data derived from the twins are expected to observe the highest professional standards of confidentiality. All VETR data are considered privileged and confidential and cannot be shared or released without prior approval from the VETR Director. In many cases, the VETR may request that the investigator obtain a Certificate of Confidentiality from the U.S. Department of Health and Human Services, to provide additional

protection for participant data. In cases of complaints of unethical practices by an investigator the VETR will contact the appropriate authorities (Institutional Review Board Officials) to request an investigation that could result in the study being halted. If the complaint is verified, the VETR will deny the investigator further access to the Registry.

All personal identifying information (i.e., names, addresses, telephone numbers) from VETR participants enrolled in a study must be returned to the VETR or anonymized, obliterated, or otherwise destroyed. The 3rd party contractor (and is some cases the investigator) must provide a letter certifying to the destruction or return of this information. Personal identifying information must be returned to the VETR when no further contact is required with the participant. Schedules for handover of participant personal identifying information can be developed according to the specific needs of each project. This policy enables the VETR to "release" a participant from a particular study and, after an appropriate respite period, make the twin approachable for invitations to participate in other studies.

2.2 Access Fees (January 2005)

The VETR is located within the Department of Veterans Affairs Epidemiologic Research and Information Center at the Seattle VA Puget Sound Health Care System. Requests from investigators, universities, and institutions impose a significant burden on VETR resources and on the VETR staff workload. For this reason, the VETR charges fees to all investigators who use the VETR. These access fees cover study-specific costs and administrative burden incurred by the VETR in support of the project, as well as recurring costs of registry maintenance. Without these fees, the resources necessary to enable investigators to access VETR participants would not be available.

- The annual access fee for applications submitted in 2005 is $35,000. The annual fee will increase 3% per year.
- VA projects have a reduced annual access fee of $20,000 in 2005. The annual fee will increase 3% per year.
- Additionally indirect costs are charged according to DHHS negotiated rates; presently (2004) the rate is 5.5%.
- For supplemental grant awards, secondary data analysis projects, and career development awards the VETR access fees are determined by the Registry Director.

2.3 Application and Review Process (January 2005)

We recommend that investigators contact the VETR project manager with requests for access as early as possible during the conceptual phase of the project. This contact will generate a dialogue about the project that will be helpful to both the investigator and the VETR. These early discussions can help clarify issues about study design and data collection methods.

2.3.1 Preliminary Application Process (January 2005)

The investigator must submit a letter of intent no longer than three pages in length summarizing the project, typically no later than three months prior to the due date for a grant or competitive renewal application. The letter of intent should be organized into the following sections: specific aims, significance, preliminary studies, and methods. Particular attention should be given to the number and characteristics of twins that will be involved in the proposed study and the data collection methodologies. Upon receipt of the letter of the intent, the VETR project manager will

contact the investigator to schedule a meeting or conference call for further discussion with the VETR Director. The VETR Director will determine the role that the VETR will play in the proposed study and may recommend that a preliminary data analysis be conducted to determine if the VETR has sufficient data/participants to support the project. In general, VETR studies are large and complex and pilot projects aimed at documenting feasibility are not an appropriate use for VETR twins. If however, an investigator requests a pilot study a brief explanation of such a request will be forwarded to the SAC for review and recommendation. The SAC will review these requests on a case-by-case basis.

2.3.2 Formal Application and Review Process (January 2005)

Once the groundwork for a project is laid through this preliminary process, an investigator can enter into the formal approval process, which includes the review of a research application (see Appendix) by the VETR SAC.

The VETR SAC consists of senior scientists who meet either by conference call or in-person to review requests by investigators for access to the VETR. The SAC provides recommendations to the VETR Director who makes the final decision on studies to be granted access. The factors considered in the decision to allow access to the VETR include:

a. The scientific merit of the proposed project.
b. The need to use VETR twins to accomplish the specified scientific aims.
c. The level of subject burden imposed on the VETR participants. Typically, access is granted only to projects that present no more than minimal risk to twins.
d. The privacy implications of the project to potential participants.
e. The project's contribution to a balanced research portfolio for the VETR.
f. The availability of funding and the potential of the project to generate long-term, significant federal and non-federal support for further study.
g. The current level of demand on the VETR staff by other research projects.
h. The potential for overlap with ongoing VETR studies.

Applicants are notified in writing of the decision within two weeks of the VETR SAC meeting date. All decisions are final and can be appealed only by revising and re-submitting the application.

3.0 Requirements for beginning an approved project (October 2002)

No research project shall be initiated without proof from the investigator that the project has received approval from the researcher's institutional review board (IRB). A copy of the approval memorandum from the appropriate IRB and a copy of all IRB-approved consent forms must be submitted to the VETR project manager. All subsequent IRB modifications and yearly-approved reviews will also be submitted to the VETR project manager.

In general, approval by the researcher's IRB will be adequate to initiate a new study with VETR twins. However, the initial contact letter by the VETR from the Registry Director for each new study must be reviewed and approved by the University of Washington IRB, which handles all human studies issues for the VETR. There may be other issues that arise in specific studies where a protocol will require additional human subjects review by the VETR.

For those studies requiring a Certificate of Confidentiality a copy must be provided to the VETR prior to the initiation of the study.

3.2 Submission of data collection instruments and protocols (October 2002)

The investigator must provide the VETR project manager with a copy of all final data collection instruments, interview scripts, and tissue collection protocols. The VETR keeps copies of all final IRBapproved materials on file to help the VETR respond to questions from participants regarding study related issues. In addition, the VETR will request to review all data collection instruments prior to final production to ensure that they conform to VETR formatting requirements. Any modifications to approved protocols must be submitted and approved by the VETR. When investigators are requesting additional data from the VETR to supplement the study data, these specific variables are to be submitted to the VETR prior to data collection.

3.3 Submission of signed agreement (October 2002)

Each investigator who is granted access to the VETR signs a formal "research agreement" delineating his or her responsibilities to the VETR in accordance with these guidelines. Issues specific to each research project will be itemized in this agreement. (An example of a research agreement is provided in Appendix xxXX). In addition, all members of the research team, including the principal investigator and 3rd party contractors, will need to sign the VETR access agreement for each new study. Access to data and/or participant information is restricted to those who have a signed research agreement with the VETR.

3.4 Payment of fees (October 2002)

The investigator must have made a partial or full payment for the project or signed a contract before the VETR will begin work or data can be released. Payment schedules will be negotiated on a project-by project basis.

4.0 Requirements for users of the VETR (October 2002)

4.1 Notification of updated contact information (October 2002)

The VETR is responsible for maintaining contact with all VETR twins. If a 3rd party contractor requires updated contact information (address and/or telephone number) the VETR will provide it to the contractor within 4 weeks of the VETR's discovering new contact information. If investigators become aware of new contact information for VETR twins during the course of a study, this information must be reported to VETR personnel.

4.2 VETR member participation (October 2002)

The VETR normally has several studies in the field at any given time. The studies vary in size, scope and duration. To accommodate the complex demands of these multiple studies the VETR has instituted a policy for the allocation of twins for field work by 3rd part contractors. Investigators coordinate with the VETR project manager on the scheduling of twin pairs for fieldwork and it typically involves dividing the study sample into a set of "batches" that are sequentially allocated. As each batch is completed the next batch is assigned to the field; once a batch has been returned to the VETR, and after an appropriate respite period, these twins can be allocated to another study. This enforces the general VETR policy that a twin cannot be involved in two studies at the same. Once the 3rd party contractor has completed a batch they are required to purge all personal identifying information from their files and provide written documentation (typically in the form of a letter) certifying this to the VETR project manager.

4.3 VETR data requests (October 2002)

Access to the VETR is granted only for the duration of data collection or funding, whichever ends first. Any VETR data made available for or collected through a proposed research project are for

use solely for the specific study. Use of data is limited to the scope of the study as it was reviewed and approved during the application process. Study data cannot be shared or transmitted to other investigators without the prior written approval from the VETR Director. Additional studies/protocols arising from VETR data must be reported to the VETR.

4.4 Notification of deviation from protocol or unanticipated risks to subjects (October 2002)

Investigators are required to report immediately to the VETR project manager any deviation from the approved research protocol that occurs during the course of the study, whether unintentional or required by study circumstances. Similarly, any discovery of unanticipated risks to twins or adverse events must be reported immediately.

4.5 Notification of twin request to withdraw (October 2002)

Investigators must notify VETR personnel within 72 hours when a VETR participant expresses a desire to withdraw from a specific study. In instances where the twin requests to be permanently removed from the VETR, the VETR project manager will contact these individuals to clarify the reasons for the request and whether and in what way they wish to be contacted by the VETR in the future.

4.6 Reporting (October 2002)

4.6.1 Biweekly Contractor Report (October 2002)

3rd party contractors and study investigators must submit a biweekly password protected electronic report in a format that is approved by the VETR. The biweekly report includes the status of each twin released by the VETR. Information typically included in the status report includes study participation, refusal and/or changes to current address. When a twin has completed a study they can no longer be contacted by the 3rd party contractor or investigator and must be returned to the VETR.

4.6.2 Annual Report (October 2002)

All researchers must submit an annual progress report to the VETR detailing the previous year's activities. Since projects have different start dates and may be linked to reporting periods established by funding agencies, a unique due date for this report will be established for each project. Annual progress reports submitted to the project's funding agency are acceptable as long as they include the components in the list below:

a. Progress in relation to original project time line.

b. Number of twins participating in the study.

c. List of presentations at professional conferences and publications in journals arising from the project (or papers in manuscript form being prepared for submission to a journal).

d. Problems or difficulties encountered, including any variations from the VETR protocol outlined in these guidelines and in the researcher agreement, and solutions to these problems.

4.6.3 VETR Publications (October 2002)

Manuscripts being prepared for submission to a journal must be submitted and approved by the VETR Director. Investigators are also asked to provide a reprint of articles published in relation to research using data from VETR participants. The VETR may also ask an investigator to

provide, on an annual basis, a brief summary of the project suitable for publication in the VETR newsletter.

4.7 Conveyance of VETR data (October 2002)

4.7.1 Completed datasets (October 2002)

At the termination of data collection or grant funding for the project, whichever occurs earlier, a complete electronic copy of all study data most be transmitted to the VETR. These data files must contain sufficient document that they can be incorporated into the VETR database for future use. The 3rd party contractors are responsible to return the datasets directly to VETR; no datasets may be forwarded to investigators. The VETR is responsible for sending datasets to the investigators according to predetermined schedules on a per study basis.

4.7.2 Personal identifiers (October 2002)

At the termination of data collection or grant funding for the project, whichever occurs earlier, names and identifying information of all VETR participants must be returned to the VETR. Personal identifying information on all computer and hard copy files must be obliterated and files must be destroyed. These measures are required to enable the VETR to maintain its promise to its participants that all possible steps are taken to protect the confidentiality of their identity and data.

5.0 Study Data (October 2002)

5.1 Specific study datasets (October 2002)

Investigators have exclusive use of data collected as part of a specific project for a five-year period following the conclusion of an approved project. During the five year period the VETR reserves the right to use data items from specific studies to perform preliminary analyses to help develop new VETR projects. At the end of the five-year period, data collected from specific projects are merged into the general VETR database. It is common for projects to need data from the VETR database to augment study specific data; the VETR provides these data to investigators but the use of VETR variables is limited to the specific aims of the approved project. Investigators must obtain approval from the VETR Director to use VETR data for analyses that differ from those specified in the original study protocol.

6.0 Acknowledgment (October 2002)

The VETR project manager will provide a suggested format for the VETR acknowledgment in manuscripts and other publications.